Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations*

Draft review available for public comment from August 02, 2012 to August 30, 2012.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Reviewer 10	Executive Summary	In the Executive Summary, (page 16, line 34), please change "include" to "included".	changed
Reviewer 10	Executive Summary	In the Executive Summary, (page 19, line 15), please change "brain jury" to "brain injury".	changed
Reviewer 10	Executive Summary	In the Executive Summary (Page 34, line 6 - 11), the authors refer to two studies but there is no reference.	We have referenced these two studies
Reviewer 1	Introduction	I think all of the areas are presented and the information is not overwhelming	Thanks
Reviewer 2	Introduction	The Introduction section was well written and organized.	Thanks
Reviewer 3	Introduction	Well written, clear, concise. The relevance of the topic to clinical practice and a clear case is made regarding the need to summarize the available evidence in order to care for patients in these special populations.	Thanks
Reviewer 4	Introduction	Well-done. The review of the history/epidemiology is good. The critical need for the study is defined and the purpose evident.	Thanks
Reviewer 5	Introduction	Well written.	Thanks
Reviewer 6	Introduction	Does an excellent job in framing the important issues and cites the sentinel research in the field.	Thanks
Reviewer 7	Introduction	All of the 8 KQs represent clinically relevant, important gaps in knowledge - they were selected on the basis of known inadequate evidence.	Thanks
Reviewer 7	Introduction	For KQ5, it should be made clear that the review applies to patients receiving chronic/long-term antiplatelet therapy - some readers might mistake the question as applying to the role of APA as thromboprophylaxis.	We have made this change in the introduction that KQ5 applies to patients receiving chronic long-term antiplatelet therapy.
Reviewer 8	Introduction	No comments	Not applicable
Reviewer 9	Introduction	This section is well written and highlight the higher risk of VTE among those with CKD.	thanks

Commentator & Affiliation	Section	Comment	Response
Reviewer 10	Introduction	Specific comments: In addition to fatal PE and PE, it might be useful to mention other nonfatal sequelae of DVT such as phlegmasia, post-thrombotic syndrome, bleeding complications from therapeutic anticoagulation, and functional impairment as well as estimate the incidence of such complications.	We appreciate the reviewers comments. The scope of this review on the comparative effectiveness and safety of pharmacologic and mechanical strategies among special populations occuring in the hospital setting. Our analytic framework clarifies that we also evaluated other outcomes such as DVT, bleeding and post-thrombotic syndrome. We had one study that reported on post-thrombotic syndrome in KQ1. However some long term outcomes such as phlegmasia and functional impairment were beyond the scope of this review. These have now been acknowledged as a limitation. We did not aim to determine the incidence of these complications which are beyond the scope of our KQs.
Reviewer 10	Introduction	Specific comments: Perhaps consider including a brief review of the mechanism of action of unfractionated heparin and low molecular weight heparin	We have added additonal text regarding the mechanism of action of these agents under “Therapies of Interest”. A full review beyond the scope of our KQs.
Reviewer 10	Introduction	"...some physicians may consider antiplatelets to be sufficient for VTE prophylaxis." Is there any evidence to support this?	We have removed this sentence
Reviewer 10	Introduction	consider mentioning the average retrieval rate in actual clinical practice of IVC filters	This is reported in the results section of KQ1
Reviewer 10	Introduction	This sentence: "Patients hospitalized with burns are at an increased risk for VTE, but there is no consensus about the most appropriate prophylactic strategy for treating bleeding in these patients." doesn't make sense to me. Why treating bleeding?	We have clarified that this refers to prophylaxis of VTE.
Reviewer 11	Introduction	Appropriately succinct.	We appreciate the reviewer’s comments
Reviewer 12	Introduction	introduction is clear, complete, and helpful.	We appreciate the reviewer’s comments
Reviewer 14	Introduction	The introduction gives a nice succinct overview of VTE and its prevention and the special populations that are the subject of this report and the relevant questions concerning VTE prophylaxis that are the subject of their meta-investigation.	We appreciate the reviewer’s comments
Reviewer 15	Introduction	No specific comments above those previously mentioned.	We appreciate the reviewer’s comments
Reviewer 16	Introduction	Excellent introduction which was very succinct	We appreciate the reviewer’s comments
Reviewer 17	Introduction	well written	We appreciate the reviewer’s comments
Public Comments – EBIR	Introduction	No comment	We appreciate the reviewer’s comments

Commentator & Affiliation	Section	Comment	Response
Reviewer 1	Methods	The specific areas are broken down in a manner that makes it very easy to understand	We appreciate the reviewer's comments
Reviewer 2	Methods	The methods section is similarly well written and organized. I was eventually able to figure out what PICOTS stands for but this should be spelled out on Table B.	**PICOTS** (**population**, intervention, comparator, outcome, timing, and setting) – We added this to the table B
Reviewer 3	Methods	The methods are clearly stated including the search strategy employed. Given the hetergeneity of the patient populations and study designs of the identified manuscripts, consistent definitions for the outcomes of interest were not constructed by the authors. Careful assessment of the methodological quality of each study included in the review was made using well accept criteria. Grading of the evidence was based on well accept criteria.	Thanks. We agree with the comment about heterogeneity of outcomes
Reviewer 4	Methods	The methodology was appropriate for the defined criteria. The IN/EXclusion criteria are sound	We appreciate the reviewer's comments
Reviewer 5	Methods	I think all of this is very well done. The table (table b) depicting the KQs was ver useulf. The uneven column spacing is distracting though, and makes it harder to compare the text across columns.	We appreciate the comments. We have fixed this uneven column spacing
Reviewer 6	Methods	I have concerns about including studies with only symptomatic VTE--most clinical episodes are asymptomatic. The effectiveness of prophylaxis cannot be assessed well with studies that only include symptomatic patients. Surveillance is necessary.	We agree with the reviewer's suggestion. We have included studies with both asymptomatic and symptomatic VTE. Asymptomatic DVT was included in our analytic framework. We attempted to distinguish between symptomatic and asymptomatic VTE and evaluate surveillance strategies. However most studies did not clarify the distinction between the two or adequately outline their surveillance strategy. Surveillance for asymptomatic PE is not used in clinical practice or research, so nowhere do we refer to asymptomatic VTE (only asymptomatic DVT)
Reviewer 6	Methods	Statistical analysis was acceptable	We appreciate the reviewer's comments
Reviewer 7	Methods	The methodology is appropriate and thorough; an iterative process using internal and outside consultants led to the KQs. Very experienced methodologists and evidence finders/Reviewers performed the reviews.	Thanks

Commentator & Affiliation	Section	Comment	Response
Reviewer 8	Methods	The search strategies and the inclusion/exclusion criteria seem reasonable. The authors do a lot of pooling of data (including, it appears, both absolute event rates as well as relative risk estimates). I do not have any specific reason to believe they have done anything incorrectly, but given the complexity of this sort of data pooling, I would suggest a statistician review this aspect of their methods in detail.	We appreciate the comments. In response, the relative risk meta-analysis in the report has now been performed independantly in two statistical programs Stats Direct and Stata to ensure consistency in results by two different analysts. For each meta-analysis, we have conducted sensitivity analysis to test the robustness of our results using alternative continuity corrections to account for the sparse data-set. This is reported as Appendix H. We draw attention to the fragility and the underlying heterogeneity of our findings when appropriate. As a result most of the SOE grades are either low or insufficient.
Reviewer 9	Methods	As stated above, please clarify if renal transplant recipients and those with nephrotic syndrome were considered for inclusion?	We excluded renal transplant patients and those with nephrotic syndrome. We have clarified this in the study selection section of the report.
Reviewer 9	Methods	Authors have considered appropriate outcome measures.	Thanks
Reviewer 10	Methods	"Are the inclusion and exclusion criteria justifiable?" - yes	Thanks
Reviewer 10	Methods	"Are the search strategies explicitly stated and logical?" - yes	Thanks
Reviewer 10	Methods	"Are the definitions or diagnostic criteria for the outcome measures appropriate?" - yes	Thanks
Reviewer 10	Methods	The statistical methods used are appropriate. The authors correctly recognize that "The studies were sufficiently heterogeneous precluding any pooling in a meta-analysis." Furthermore, the evidence grading schema is appropriate.	Thanks, We agree with the comment about heterogeneity. We have only pooled studies when appropriate and have provided several sensitivity analysis
Reviewer 10	Methods	"concealed the assignment until requirement was complete." Do you mean "recruitment"?	We have modified this sentence to read concealed the assignment until randomization was complete.
Reviewer 10	Methods	change "evidence based" to "evidence base"	This has been fixed
Reviewer 10	Methods	Was non-English publication language an exclusion criteria?	We did not exclude articles based on language.
Reviewer 11	Methods	The study eligibility criteria are logical and justifiable.	Thanks
Reviewer 11	Methods	The assessment of adverse events and complications is challenging since it is heterogeneous across different studies and since many of the complications reported are of uncertain clinical importance (e.g. "perforation" of filter legs, filter tilting, asymptomatic DVT, etc.).	We agree and have accordingly interpreted the data on adverse effects cautiously. We believe that including such adverse events and complications is important for a balanced review of efficacy and safety.

Commentator & Affiliation	Section	Comment	Response
Reviewer 11	Methods	On imaging studies, it can be difficult to tell whether or not a filter leg/strut has really "perforated" the caval wall versus is just tenting the wall from within. As such, the reporting of this outcome is undoubtedly fraught with error and heterogeneity.	We agree and have accordingly interpreted the data on adverse effects cautiously. However we believe that including such adverse events and complication is important for a balanced review of efficacy and safety
Reviewer 11	Methods	Filter-related thrombosis is also a very difficult outcome to report. We simply do not know whether the occurrence of thrombus within an IVC filter represents a device-related complication (e.g. the filter promoted thrombosis) versus a major success of the device (e.g. the filter did what it was supposed to do - it trapped a large embolus). Also, the patient impact of filter-related thrombosis is unclear - it can be entirely asymptomatic versus cause significant symptoms in the legs and lower body. Accordingly, for a comparative effectiveness review that seeks to influence clinical practice, I believe this should either be excluded as an "outcome" or the results embedded within a nuanced description of this challenge.	We share some of the reviewers concern regarding the description of filter related thrombosis. Despite these concerns we believe that such outcomes should be included with a nuanced description of these challenges. This is described in the results section where we describe the results from the uncontrolled studies for KQ1. Filter thrombosis was not described as an outcome for any of the other KQs.
Reviewer 12	Methods	yes to all the questions. Very detailed and completely stated strategies and clear definitions.	Thanks
Reviewer 14	Methods	I think the inclusion and exclusion criteria are justified. The search strategy is explicitly stated and logical. The definitions and diagnostic criteria are appropriate. The statistical methods are sound.	Thanks

Commentator & Affiliation	Section	Comment	Response
Reviewer 15	Methods	See comments above re: formulation of questions which i found, in many circumstances, very tangential to the questions that clinicians would want answered. The search strategy was, no doubt, comprehensive and this document will serve as a great source of references. The presentation of forest plots, or forest-like plots for much of the data, which seem pretty poor, is questionable. They have an aura of respectability which does not honour the garbage-in garbage-out feeling of the underlying data.	We appreciate these comments, especially regarding our search. These KQs were formulated after several rounds of expert and clinical input including a transparent public comments process. The panel and public comments agreed with the importance of these specific KQs among these special populations. Most of the data was not pooled in a meta-analysis for 6 of the 8 KQs. Only a small minority of data on IVC filters from KQ1 and KQ8 was pooled when it met prespecified criteria for pooling such as the requisite number of comparative studies which reported data on outcomes of interest. We draw attention to the limitations of the underlying sparse data in the report. Accordingly, several sensitivity analyses were also carried out to test the robustness of these results in two separate statistical programs. The data have been interpreted the data cautiously as reflected in the majority of our SOE grades being either low or insufficient.
Reviewer 16	Methods	The inclusion and exclusion criteria and search strategies were appropriate.	Thanks
Reviewer 17	Methods	inclusion and exclusion criteria are justifiable	Thanks
Public Comments – EBIR	Methods	The paper seems to be methodologically sound overall. See our comment below on the Limitations paragraph of the Discussion, regarding the number and type of Reviewers involved for selecting the abstracts and grading the evidence from the source articles.	See our response to the grading segment below
Public Comments – EBIR	Methods	The authors are to be congratulated on their thorough search and analysis. Thanks to their inclusion of many studies with designs other than just randomized controlled trials (RCT), the paper appears very comprehensive. In a field where level I evidence is scarce, we believe that neglecting lower level of evidence could have been detrimental to the analysis and its conclusions.	Thanks. We agree that studies other than RCTs are informative for these special populations. We have included such studies.
Public Comments – EBIR	Methods	Page 16 (page 56 of 164 in PDF document): “After synthesizing the evidence, two Reviewers graded the quantity, quality, and consistency of the best available evidence addressing KQs 1 to 8 by adapting an evidence grading scheme recommended in the Methods Guide for Conducting Comparative Effectiveness Reviews”: Was this grading done separately and independently by both Reviewers? How were disagreements between Reviewers resolved?	This was done independently by two reviewers. Disagreements between the two reviewers were resolved through consensus and adjudication by a third reviewer. Reviewer pairs included members with content and methods expertise.

Commentator & Affiliation	Section	Comment	Response
Reviewer 1	Results	Your review was spot-on. The critical analysis of the data is exactly what is needed. There are still questions as to what this difficult group of patients need and this outlines where further studies need to go.	Thanks
Reviewer 2	Results	The Results section is great up until it gets to summarize the results by population. Over and over again there are bullet points that all say "the strength of evidence is insufficient to support..." There must be a more concise way to do this. How about saying what, if anything, the strength of the evidence is sufficient to do and then give a concise bulleted list of the things it is not sufficient to do. I found an error in Table 21, the rates of VTE are reported as rates of PE in the Birkmeyer et al study.	We have made our SOE statements more concise. For example, for KQ2b we now say " The strength of evidence was insufficient to comment on the effectiveness of early (< 72 hours) versus late (> 72 hours) pharmacoprophylaxis with enoxaparin, UFH or any heparin on the outcomes of VTE, DVT, PE, fatal PE, total mortality, major and minor bleeding. " We have corrected the error in the Table for this study based on the updated data.
Reviewer 3	Results	The result for each key question is described in sufficient detail - including the characteristics of the identified studies. Tables and figures are sufficiently detailed and provide further support to the narrative summaries.	Thanks
Reviewer 4	Results	I believe the results are on track. The message is clear in each of the KQs. I could not find a study that I would have included/excluded that was not already in the review.	Thanks
Reviewer 5	Results	I see no major problems. The review is so large that the amount of detail offered is skimpy at times. It makes me wonder if the results might be better presented in a few different summaries.	We have now provided a concise Executive Summary
Reviewer 6	Results	The tabulated data were helpful in assessing both the methodological rigor of cited studies and the outcome.	Thanks
Reviewer 6	Results	The investigators were very thorough in their search and I did not notice any omissions	Thanks
Reviewer 7	Results	The results are clearly presented (but tedious). Overall, only 2 randomized trials were found for all of the KQs (neither high quality). Of the 52 KQ/intervention/outcome reviews conducted, 50 were subject to high risk of bias, 2 were at moderate bias risk and none had a low risk of bias. Of the 77 individual study/outcome measure combinations for the KQs, 97% exhibited high risk of bias. 61% of all the studies included pertained to KQ1. The studies were also so heterogeneous that formal pooling was not possible for any of the questions. For KQ3, should specifically state that no studies assessing thromboprophylaxis were found. For KQ6, the 1st 4 key points deal with the rather unimportant issue of IVCF use rather than the much more important issues related to primary prophylaxis.	We have described the risk of bias among included studies as an appendix. The updated search has now identified 6 RCTs for all these KQs In KQ3, we identified one study without a comparison group that described use of IVCF; this is described. We describe what we found in the literature for KQ6. 12 of the 21 studies included studies described the use of filters in this population. The order of the key points parallels the order in which the studies are described in the text.

Commentator & Affiliation	Section	Comment	Response
Reviewer 8	Results	Amount of material in the results is certainly adequate and the tables are quite helpful. I do not think the investigators overlooked any critical studies.	Thanks
Reviewer 9	Results	They have appropriately summarized the 5 studies that have provided relevant details. There seems to be no selection bias involved.	Thanks
Reviewer 10	Results	"Is the amount of detail presented in the results section appropriate?" - yes	Thanks
Reviewer 10	Results	"Are the characteristics of the studies clearly described?" - yes, in exquisite detail	Thanks
Reviewer 10	Results	"Are the key messages explicit and applicable?" - yes to the extent that the patients in the studies reflect the typical population	We agree and have discussed this issue of applicability of the studies to the target population
Reviewer 10	Results	"Are the figures, tables, and appendices adequate and descriptive?" - yes	We appreciate the reviewer's comments
Reviewer 10	Results	"Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded?" - not to the best of my knowledge	Thanks
Reviewer 10	Results	What was the span of publication year for included studies?	We did not have any date restrictions for databases. Our search was limited till July 2012
Reviewer 10	Results	How many studies needed to be adjudicated? What was the outcome of the adjudicated studies?	Our process requires dual review to assure accurate data extraction. We resolved all conflicts via adjudication by a third reviewer We do not track the number of studies requiring adjudication.
Reviewer 11	Results	The Results section is fine.	Thanks
Reviewer 12	Results	I did not determine that there were any studies overlooked. Very detailed.	Thanks
Reviewer 14	Results	The authors present the results in a logical manner with appropriate detail. The authors provide sufficient detail to allow the reader to assess the individual studies design weaknesses. The authors display study data in tables and figures in an easily understandable way. I think the authors have included all the important studies published on the various questions considered in their review.	Thanks
Reviewer 15	Results	There is massive duplication throughout the document. The very poor data seems to make such massive documents, and such in depth turning over of poor quality data, seem a bit excessive.	We have edited the document to make it more concise
Reviewer 16	Results	The results section and tables are over the top (this is a positive comment). There is so much data and this provides a gold mine for developing projects in quality improvement and safety. I did not note any papers overlooked by the investigators.	Thanks. We agree with the authors
Reviewer 17	Results	excellent description of studies	Thanks
Public Comments - EBIR	Results	No comment	No response

Commentator & Affiliation	Section	Comment	Response
Public Comments - EBIR BJ	Results	I have concerns regarding your data and conclusions for KQ1. I have reviewed this literature as well and have problems with including the Rogers studies in your meta-analysis. There are 2 studies by Rogers that you count separately, but probably include many of the same patients (one is trauma and 1 is ortho trauma, but both are same years, same institition, same first author). Is it fair to "double count" these patients? These are also two (of the three) studies that suggest PE, fatal PE, and mortality are more likely with IVC filters. These Rogers studies had major limitations and used historical controls and had so many more patients who were not that injured in the control group. I just don't believe it is true.	We appreciate these comments and have substantially revised KQ1 and the report to respond to these concerns regarding the issue of double counting and other methodological limitations such as imbalance in prognostic factors in the two Rogers studies. We agree that these studies appear to be fatally flawed outliers. We therefore decided to exclude these two studies (provide PMID) and after exclusion of these studies, the updated SOE and meta-analysis shows a low SOE for reduction of PE and fatal PE with IVC filters in KQ1.
Reviewer 1	Discussion	The restrictions are clearly stated.	Thanks
Reviewer 2	Discussion	The discussion section is also confusingly worded in parts. For example, "In each of the studies that we included, physicians ultimately removed more than two-thirds of the retrievable filters placed. Because bariatric surgery requires close followup and medical compliance, there may be relatively high rates of filter retrieval in this patient population and a lesser likelihood of longterm filter-related complications." I don't believe this to be true and it is inaccurate to the extent that Birkmeyer study does not report the rate of retrieval of retreivable filters. Another example, "Birkmeyer et al observed an attenuation of the unadjusted association between the use of IVC filters and adverse clinical outcomes after propensity score adjustment. This suggests that the process of selecting patients for filters based on VTE risk may bias toward a lack of filter efficacy, or the appearance of harm." I'm not sure what this was trying to say but the study showed a lack of effectiveness of IVC filters among patients undergoing bariatric surgery and potential harms associated with the practice. To address the selection bias issue, the authors recently conducted a propensity matched analysis which was one of the top ten studies presented at the ASMBS meeting this year. The authors are still working on the paper. The authors also recently conducted a study of the comparative effectiveness of unfractionated and low molecular weight heparin for the prevention of VTE in bariatric surgery which is in press at Archives of Surgery. Hopefully, the addition of these two studies will allow the report to say something somewhat stronger with regard to the evidence on these two issues.	We appreciate that the reviewer has shared these papers. We cannot include the pre-publication study data, as this was not part of our protocol. If and when this review is updated, we will be able to include these data. We clarified the language in the discussion where the reviewer noted some confusing sentences.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	Discussion	To my knowledge, no important literature has been omitted from the review. The findings are clearly stated. The limitations of studies included in the review are discussed in sufficient depth. However, the limitations of the SYSTEMATIC REVIEW were not discussed in great depth (indeed, only 2 sentences!). It should also be acknowledged that unpublished data was not sought or included in this review. (Although, admittedly, unpublished data is unlikely to have impacted or influenced the findings).	We appreciate the reviewer's comments. We requested and reviewed Scientific Information Packets (SIPs) from the pharmaceutical manufacturers as a source of unpublished data. The yield is described in the results (scant). We have expanded on the limitations of the systematic review in the discussion. "Although our search strategy was comprehensive, we may have missed studies. Although we included study designs other than randomized controlled trials in our review, the identification and indexing of observational studies is far more challenging than that of randomized controlled trials. It is possible we may have missed a few observational studies. The potential impact of this on the strength of our inference is unknown. We were unable to assess the possibility of publication bias or selective outcomes reporting and its impact on our findings, and it is difficult to determine the impact of unpublished data on the findings of the systematic review."
Reviewer 4	Discussion	The interesting aspect of 'future research' is the fact that it all must rely on massive RCTs to be effective. The trauma population, in particular, is difficult to translate to RCT capability. I would consider making the cohort studies more a priority (ie, multi-center, each center sticks to bias and compare, etc.)	We agree. We have revised the future research section to include the need for more observational studies which are more realistic and pragmatic for these special populations
Reviewer 5	Discussion	The discussion is good. Future research requirements are spelled out, but perhaps registry data could help us (as opposed to RCTs) for some of these questions, as some of the proposed RCTs may never be done.	We agree have revised the future research to emphasize the usefulness of such registries.
Reviewer 6	Discussion	The implications of each question are clearly stated and are well summarized	Thanks

Commentator & Affiliation	Section	Comment	Response
Reviewer 7	Discussion	This CER summarizes the extent of knowledge for 8 thromboprophylaxis subtopics but provides no new evidence or insights. The suggestions for further research in the topic areas are rather superficial while they should be the key discussion point of the report.	We appreciate the reviewer's comments and think that the absence of strong evidence may be the most impactful outcome of this review. We tried to make the future research section actionable with concrete recommendations for studies that are feasible and that would contribute importantly to this evidence base.
Reviewer 7	Discussion	The principal recommendation for KQ1 is to conduct a large multi-center RCT of IVCF in trauma. Given the low rate of clinically-important PE in trauma patients who receive currently available prophylaxis, the incredible heterogeneity of trauma patients and the sample size in the thousands, a methodologically-appropriate RCT is not possible and will never be carried out. Suggest the authors change the language to something like "Ideally, it would be nice to have a well-done RCT addressing this question. However, this is unlikely to ever be done. A carefully matched cohort study of trauma patients who are provided the "best" thromboprophylaxis that can be provided and compared to a similarly prophylaxed cohort of patients who also received an IVCF might provide some further insight into this controversy."	We agree. We have revised the future research section to include the need for more observational studies which are more realistic and pragmatic for these special populations including KQ1
Reviewer 7	Discussion	For KQ2, a double-blind RCT of early vs delayed initiation of anticoagulant prophylaxis in patients with TBI is feasible and should be done but was not a suggestion of the authors.	Yes – we said that trials may be important and have added "including trials about the timing of initiation of prophylaxis."
Reviewer 7	Discussion	For KQ3, the authors recommend further study of the burn area as a predictor for VTE. That's fine but what they really should recommend is better quality studies to assess the specific risk factors for VTE in burn patients including burn area but also including age, BMI, concomitant injuries, mobility status, central venous lines, prophylaxis use, etc.	We did not systematically search for studies about VTE risk factors in burned patients (only about prophylaxis of VTE) so we cannot really address whether additional research on this topic is needed.

Commentator & Affiliation	Section	Comment	Response
Reviewer 7	Discussion	For KQ6, the authors suggest a RCT of IVCF in the highest risk bariatric patients - even mention of this should be reconsidered since such a study is definitely not feasible and there are several, much more important clinical questions related to prophylaxis in these patients (various higher doses of LMWH, LMWH vs SCD vs combination, duration of prophylaxis).	We agree and have revised this to suggest that a trial of IVCF may not be warranted. We urge the need for trials to assess various doses and duration of pharmacoprophylaxis. "Trials of IVC filters in patients undergoing bariatric surgery might not be warranted. There is established value of pharmacologic prophylaxis in this patient population, so that RCTs that do not allow pharmacological treatment might be considered to be unethical. Similarly, because the rates of events are so low in patients with pharmacological treatment, exposing individuals to filter placement in an RCT may expose them to complication risk while there is little opportunity to demonstrate improvement in PE rates over the existing low rates. Such trials should include only those patients deemed to be at highest risk for VTE complications, such as those with prior VTE. RCTs might address whether standard doses of prophylaxis that have been proven safe and effective in other types of surgery (such as 5,000 units of subcutaneous unfractionated heparin three times daily, enoxaparin 30 mg twice daily, or enoxaparin 40 mg once daily) are adequate for patients undergoing bariatric surgery. We suggest that weight-based dosing compared to fixed-dosing, rather than BMI-based dosing compared to fixed-dosing, is the more relevant scientific question. "

Commentator & Affiliation	Section	Comment	Response
Reviewer 7	Discussion	For KQ7, I don't agree with the recommendation to do RCTs of weight-based or BMI-based anticoagulant dosing except in obese patients only.	We agree that this statement was too general and did not reflect what we intended. We specify that weight-based dosing might be important in the bariatric population: "We suggest that weight-based dosing compared to fixed-dosing, rather than BMI-based dosing compared to fixed-dosing, is the more relevant scientific question."
Reviewer 8	Discussion	The implications are clearly stated but they are sobering - we have almost no good-quality evidence to inform the key clinical questions these authors set out to answer. I think the future research section of the executive summary could be further expanded to include more specific suggestions about the design and size of the sorts of trials that would be needed to address some of the outstanding clinical dilemmas.	We have revised the future research section of the executive summary to highlight some of these issues.
Reviewer 9	Discussion	Given the dearth of high-quality evidence about the use of VTE prophylaxis, authors have refrained from drawing any firm conclusions. This is reasonable and argues for future studies on this topic.	We appreciate the reviewer's comments.
Reviewer 9	Discussion	Conducting a large clinical in those with CKD might expensive and difficult given the lack of data on both risks and benefits of different therapeutic options. Thus it would useul to detail the specific type of studies that might be conducted in kidney disease population (similar to what have been recommended for other population in this report - like propensity matched analysis).	We have clarified that for the renal failure population, it might be more useful to have adeqaute data on subgroups from large RCTs
Reviewer 10	Discussion	"Are the implications of the major findings clearly stated?" - yes	Thanks
Reviewer 10	Discussion	"In the discussion, did the investigators omit any important literature?" - to the best of my knowledge, no	Thanks
Reviewer 10	Discussion	Are there any currently registered trials on these topics on clinicaltrials.gov?	We have included such a list of clinical trials registered on these topics in the results section on clinicaltrials.gov These are describing in Appendix I. We reviewed these when writing the FRN section and have now also described in Appendix I whether the studies in progress or recently completed obviate the need for additional research.
Reviewer 10	Discussion	The authors should be more emphatic about the urgent need for high-quality studies and the non-need for more poor-quality studies at high risk of bias. Additional single-center retrospective reviews do not add useful information to the literature and represent a waste of time, money, and effort. They should call on specific organizations (eg: AAST, SCCM, ARDSnet, etc.) to make this research a priority.	Our future research section highlights the need for better quality studies for these specific populations. It is outside of our purview to call upon specific organizations.

Commentator & Affiliation	Section	Comment	Response
Reviewer 10	Discussion	"Is the future research section clear and easily translated into new research?" - The authors clearly define the deficiencies and make suggestions for future research. However, I find this section lacking. I have read many reviews and articles where the authors make similarly broad and generic recommendations. After such an exhaustive and high-level systematic review of the literature, I would consider the authors to be foremost experts on this topic. Therefore, as a reader, I would like to have the authors design a theoretical study. For example, based on their review of the literature, what sample size would be required to perform a high-quality RCT in bariatric surgery? In underweight? In renal failure? Based on the average census of these special populations in the average hospital, how many centers would be required to perform such a study?	We agree that RCTs may be impractical or not feasible in many instances. We have revised the future research section to outline what specific study designs appropriate for each KQ. This section outlines the strengths and limitations of various designs such as cohort studies using instrumental variables vs subgroup analysis of RCTs. We provide specific details of confounders that should be considered for some of the KQs. Details regarding the sample size of such studies are context specific and beyond the scope of this report.
Reviewer 10	Discussion	"Are the limitations of the review/studies described adequately?" - yes	Thanks
Reviewer 11	Discussion	The limitations are well-summarized and the future directions for research are clear.	Thanks
Reviewer 11	Discussion	The "Future Research" section should be sure to include post-thrombotic syndrome (PTS) as an important outcome to be studied. This is particularly important for filter studies. For example, if a filter study shows reduced PE but greater recurrent DVT, the ultimate value of the intervention may hinge on the degree to which the recurrent DVT episodes actually affected the health of the patient (i.e. by resulting in long-term sequelae from PTS). A DVT that did not cause PE or PTS is a minor problem, but not a major adverse outcome.	We have significantly expanded the future research section recommendations for KQ1 and other KQs. We have specified the need for long term studies on post-thrombotic syndrome.
Reviewer 12	Discussion	Yes the future research section is very clear and translatable. Implications are very explicit. Limitations carefully stated.	Thanks
Reviewer 14	Discussion	The authors have done a comprehensive review of a collection of important but inadequately investigated topics in VTE prevention. The discussion clearly identifes the most important gaps in the existing knowledge base and what studies should be done to address these deficiencies.	Thanks
Reviewer 15	Discussion	The future research areas could posit very specific questions: Does the use of unfractionated heparin reduce DVT/PE compared with XYZ would be a great way of framing future research. Less explicit instructions run the risk of breeding more low quality evidence.	We have substantially revised the future research to be more specific about the study questions for each population. It is highly unlikely that specific RCTs will be conducted on all these special populations. We have made recommendations regarding the observational designs that would be most useful

Commentator & Affiliation	Section	Comment	Response
Reviewer 16	Discussion	The directions for future reseach are clear. As always the key issue will be funding research in special populations. This data will provide the basis for proof of concept for trials with the new oral anticoagulants. I did review a study on the dabigatran for VTE prophylaxis in orthopedic surgery. Friedman et al showed that in the 4 dabigatran trials patients on dabigatran plus ASA or NSAID did not bleed more than those not on these agents. Thromb Haemost 2102;108:183-190. I thought of mentioning this because of the section special groups with antiplatelet therapy.	Thank you –we have included this study now in our review – for KQ5.
Public Comments – EBIR	Discussion	The paragraph on limitations underlines very few (2) possible weaknesses of the white paper. One limitation that could, and perhaps should, be stressed is that only two reviewers were involved in many of the steps of the work (e.g., abstracts selection, and grading of study findings), and their areas of expertise are not disclosed; a larger, well-balanced group (i.e., a group with representatives from multiple medical specialties, patients advocates and representatives from the general public, etc.) might be useful for readers to assess any potential bias of the reviewers themselves.	We have expanded on the limitations of the systematic review. We have also clarified the expertise of the reviewers so that readers can assess their potential biases. Two independent reviewers, one with methodologic expertise and other with clinical expertise in the relevant domains were involved in each step of the systematic review process. This is considered standard for systematic reviews. It is unknown if drawing from a larger sample of reviewers would result in alternative inferences or minimize potential biases. It is more important to have a structured protocol and transparent process of reporting results as we have done in this report.
Public Comments – EBIR	Discussion	Also, this white paper draft, despite being open to the public for comment on the web, could be actively sent and circulated directly to different scientific societies and patient advocacy groups that might be interested in it. Doing this would help to promote agreement by interested and invested parties, as well as to provide more feedback to the authors.	We appreciate the reviewer's comments. We actively solicited comments from the experts as shown in the number of comments received.
Public Comments – EBIR	Discussion	The authors did a great job at showing the lack of sufficient evidence and the need for more data, while avoiding the trap of bluntly rejecting some of the widely promulgated therapies for patient populations with VTE.	We appreciate the reviewer's comments and agree that our conclusions reflect the data.
Public Comments – EBIR	Discussion	In the paragraph on "Future Research" (page 112, which is page 152 of 164 in the PDF document), the fifth sentence appears to be incomplete: "34The American Venous Forum and the Society of Interventional Radiology Multidisciplinary Consensus Conference which has placed a high priority on studies of IVCFs in trauma34".	We have modified this sentence
Public Comments – KI	Discussion	Key Question # 1 IVC Discussion: Need to differentiate IVC and PE prevention from DVT	We have made this distinction clear

Commentator & Affiliation	Section	Comment	Response
Reviewer 17	Conclusion	outstanding job stating the conclusions and describing how this can be translated into further research	Thanks
Reviewer 3	Figures/Tables	One omission - Table 2 - Pharmacological agents approved in the US. Desirudin (Ipravask) is a direct thrombin inhibitor that was approved by the FDA in April 2003 for DVT prevention in patients undergoing elective knee replacement surgery. However, the agent was not available until January 2010. This agent was not listed in the table and it is unclear if the literature search included this agent. My own quick review of the literature failed to reveal any manuscripts relevant to this review which used desirudin in one of the special populations covered in this comparative effectiveness review.	We included in our search strategy (Desirudin[nm] OR Desirudin[tiab] OR Iprivask[tiab])OR
Public Comments – EBIR	Figures/Tables	The ISS (Injury Severity Score) is defined below Table 6 but not earlier (e.g., in Table 4, or in the text, where it first appears on page 30 (i.e., page 70 of 164 in the PDF document).	This has been fixed
Public Comments - EBIR	Figures/Tables	Figure 4: If the report of Rogers FB et al. from 1995, it is possible that IVC filters may actually have proven benefit in preventing fatal PE in the trauma population. That article was a retrospective, historical comparison that included a group of 63 patients with filters and another group of 2,525 control subjects with no specification on age, gender and ISS scores. As pointed out by the authors of the present white paper (bottom of page 24, or page 64 of 164 in the PDF document), “Rogers et al. 1995 contributed to substantial statistical heterogeneity. Sensitivity analysis after exclusion of this study showed a precise and consistent evidence of reduction in fatal PE with IVC filters compared to no IVC filters, without any evidence of statistical heterogeneity (RR, 0.09,95% CI 0.01 to 0.81; I2=0%).“	We agree with the reviewer’s suggestion about the potential problems with the Roger’s study including duplication and unbalanced ISS scores. We have now excluded these two fatally flawed studies. After excluding these studies there was low SOE to support that filters reduce PE and fatal PE
Public Comments – EBIR	References	No Comment	Not applicable
Public Comments – EBIR	Appendix	No Comment	Not applicable
Reviewer 1	General	I think this is a great review of some very difficult literature.	We appreciate the reviewers comments
Reviewer 2	General	Reading this report was really tough. The language is sort of tortured. For example (pg.23 in the Results by Population section, "The strength of evidence is low supporting that prophylactic inferior vena cava filters increase the risk of post-operative DVT relative to no filters, in patients also receiving non-invasive mechanical measures and pharmacological prophylaxis. We based this rating on consistent and precise estimate of increased risk of DVT with filters compared to no filters (RR = 2.28, 95% CI=1.06 to 4.94)." Does this mean that filters increase or decrease the risk of DVT? It looks like they do and the report says that the rating is based on a consistent and precise estimate, yet the report says the strength of the evidence is low to support that they do. Would it be clearer to say that filters seem to increase the risk of DVT, however most of the studies were of poor quality?	We appreciate the reviewer’s comments The SOE is distinct from quality or risk of bias of included studies as it included additional considerations such as directness, precision and consistency. We have modified our SOE statement to make it user friendly.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	General	The Statement of Funding and Purpose indicates the intended audience of the systematic review. There is no subsequent statement by the review's authors regarding the intended audience. The key questions are explicity stated and clinically relevant.	We appreciate the reviewer's comments. The intended audience of this review is various guideline makers, policy makers and clinicians
Reviewer 4	General	The overall report is clinically meaningful. The target population and audience is defined appropriately and the key questions explicit. Each of the KQs take on an area of current interest within the realm of VTE prophylaxis.	We appreciate the reviewers comments
Reviewer 5	General	The questions are well framed and meaningful. The lack of guidance for these important questions is frustrating, but this is just reflecting the poor state of the literature.	We appreciate the reviewers comments
Reviewer 6	General	The report is clinically meaningful because it demonstrates that the evidence supporting much of what we do with prophylaxis has a very wak evidence base and that much work must be done to strengthen the evidence base. To address some questions the target population was well defined, but in others not so well define--ISS is helpful for the trauma population, but for TBI GCS is not as useful as either head AIA or a CT scoring system--these were not consistent .	We extracted information on specific injury scores by region (Head/neck AIS) when it was available for KQ2
Reviewer 7	General	This CER identified 8 important areas of thromboprophylaxis where there is no clinical consensus as a result of inadequate (and, in some cases, no) evidence. After an exhaustive review and numerous analyses, the report is also limited by this same paucity of evidence.	We appreciate the reviewer's comments. We agree that the quality of evidence, precludes definitive conclusions for many of the KQs
Reviewer 8	General	The report is as clinically meaningful as the poor-quality evidence would permit. For many of the key questions, insufficient evidence was found to support any answer - this is not the fault of the authors but it limits the utility of the report for clinicians faced with making institutional or individual patient decisions.	We appreciate the reviewer's comments. We agree that the quality of evidence, precludes definitive conclusions for many of the KQs
Reviewer 9	General	Following are my comments relating to KQ-8 where in the authors examined the effects of VTE prophylaxis in those with different severity of kidney disease. In general, this is a well-conducted systematic review on a relevant topic that has high clinical relevance.	We appreciate the reviewers' comments. We agree that the quality of evidence, precludes definitive conclusions for many of the KQs
Reviewer 9	General	Authors seem to have included those with acute kidney injury, chronic kidney disease and those on dialysis. Did they consider renal transplant recipients as well as this group are at higher risk for DVT and also at higher risk for bleeding due to potential drug interactions?	We did not include patients undergoing renal transplant. This has been acknowledged.
Reviewer 9	General	Patients with nephrotic syndrome are at very high risk for venous thromboembolism. Did they consider this population in the search strategy? It might be worth stating that this population was not specifically considered if they did not consider those with nephrotic syndrome.	We did not include patients with nephrotic syndrome. This has been acknowledged.
Reviewer 10	General	Is the report clinically meaningful? - While the question posed by the investigators is extremely relevant and meaningful, the conclusions stated do not serve to inform the clinician nor do they impact current clinical practice. This is through no fault of the authors, but rather to the paucity of quality data available.	We agree with the reviewer about the paucity of data.

Commentator & Affiliation	Section	Comment	Response
Reviewer 10	General	"Are the target population and audience explicitly defined?" - Yes, the authors do an excellent job of identifying their target audience: "The results of this comparative effectiveness review will inform those developing guidelines for the care of these patient populations. This report should also be useful to clinicians and patients who are making decisions about the best approach to prophylaxis."	We appreciate the reviewer's comments.
Reviewer 10	General	"Are the key questions appropriate and explicitly stated?" - yes, the key questions are appropriate and explicitly stated. There is one notable absence though. I find it odd that the authors did not explicitly ask the key question regarding comparative effectiveness of pharamcologic and mechanical prophylaxis in trauma patients WITHOUT traumatic brain injury. They review the literature on IVC filters in all trauma patients as well as pharmacologic and mechanical prophylaxis in brain injured patients. Additionally, there are other high-risk sub-groups within the trauma population: spinal injury, multiple extremity fractures, pelvic fractures, etc. which may be useful to consider.	We appreciate the reviewer's comments. However it was the general view of the experts involved that other guidelines such as the ACCP had clearly established the role of pharmacologic therapies in other patients with trauma, Other subgroups of trauma patients should be explored in future reviews. However, the role of IVC filters among patients with trauma, and the timing of therapy among patients with TBI were felt to be the highest priority KQs.
Reviewer 10	General	Since the authors excluded Children, Pediatric, and Adolescent, perhaps consider including the word "Adult" somewhere in the title.	We appreciate the reviewer's comments. At this stage, it will be difficult to change the title of the report.
Reviewer 11	General	Yes, the target audiences are well-defined.	Thank you
Reviewer 11	General	The justification to separately consider patients with trauma, traumatic brain injury, burns, antiplatelet therapy, renal failure, and bariatric surgery is clear to me since the risks of anticoagulant drug-based strategies is certainly higher in these groups.	We appreciate the reviewer's comments
Reviewer 11	General	I am less certain that patients with liver disease or obese/underweight really justify separate consideration.	We appreciate the reviewer's comments. However these KQs were developed after a transparent process which included public posting.
Reviewer 12	General	Yes, the subpopulations reviewed are precisely those for which there is little available information and yet VTE is a common concern. The target population is explicitly defined and the key questions appropriate and explicitly stated.	We appreciate the reviewer's comments
Reviewer 14	General	Sharma and Singh and colleagues have produced a highly detailed comprehensive analysis of several outstanding unanswered questions in the realm of VTE prophylaxis - the risks and benefits of different pharmacological and mechanical approaches to prophylaxis in special subpopulations of hospitalized patients. Their report indicates that the available literature is very limited in terms of quality regarding a number of important questions in VTE prevention. They clearly identified their target populations and the clinical audience. Their key questions are appropriately and explicitly stated. Their conclusions are important- a great deal of work remains to be done to identify the optimal approach to VTE prevention in these special but not uncommon patients.	We appreciate the reviewer's comments

Commentator & Affiliation	Section	Comment	Response
Reviewer 15	General	This is a very comprehensive review. Its length makes it almost incomprehensible. Taken with the various formatting and grammar issues (as below) it is difficult or impossible to read. Certainly I do not see clinicians ever using a document like this - with many ways to spend their time this is not going to be high on their list.	We appreciate the comments. We have revised and formatted the document to make it more user- friendly and shortened the executive summary. We have also edited it for clarity. This report will be translated by the SRC into a user friendly version for clinicians.
Reviewer 15	General	The questions are framed oddly, and some obvious ones are missing. Why wouldn't the questions be something along the line" Do IVC filters cause or prevent VTE in trauma patients?" In my opinion as someone who writes and publishes high impact systematic reviews and guidelines these could be much more clearly written, systematically presented, and digested for the reader.	However these KQs were developed after a transparent process which included public posting. Unfortunately at this stage it is not possible to change the format of the KQ.
Reviewer 15	General	This would be much better presented as a whole series of smaller reports on each of the areas with data, and perhaps a single report presenting all the areas with no data.	We appreciate the comments. We plan to publish manuscripts in a series of smaller reports
Reviewer 15	General	Page 69 of the PDF (page 27 of the document) - "The overall rates were uniformly low to allow any meaningful analysis" - I presume a word is missing.	We have revised this sentence.
Reviewer 15	General	English style is odd throughout. Perhaps this is normal for these documents. For example, throughout, there are phrases such as "The strength of evidence is insufficient that prophylactic IVC filter placement when compared to no filter use is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma." I would have thought this should say "The strength of evidence is insufficient TO CONCLUDE that prophylactic IVC filter placement when compared to no filter use is associated with a lower incidence of PE and fatal PE in hospitalized patients with trauma." Similarly "Despite that patients with compromised renal function who require pharmacologic VTE prophylaxis are highly common; we found insufficient evidence to guide treatment decisions." The semi-colon (used in this setting in many places) is actually unneeded. It actually makes the sentence harder to understand.	We appreciate the reviewer's comments. We have modified the SOE statements accordingly.
Reviewer 15	General	I would suggest that the entire document be proofread as there are numerous such situations.	We have edited the document and proof-read it for clarity.
Reviewer 15	General	It is not clear to me why there is such redundancy throughout the text. The questions are restated many, many times. The same paragraphs appear many, many times. For some areas with no evidence that is restated many times. It looks like this is the work of a whole bunch of committees and no one person has spent the many many hours that would be required to knit it all togehter.	We have tried to eliminate redundant text throughout the report to the extent that is possible.
Reviewer 16	General	The report makes me nervous as a clinician since the evidence is not as good as I always believed for these populations. This does not mean that we do not have an approach to managing this group of patients. As the studies clearly point out.	We share the reviewers concern about the lack of high quality evidence for several of the KQs

Commentator & Affiliation	Section	Comment	Response
Reviewer 17	General	This report is clinically meaningful. The authors have done an outstanding job reviewing the material and coming to conclusions. They have clearly defined the target populations and the audience. Their key questions are all appropriate and well written. I only have one comment. Since this extensively looked at VTE prophylaxis I wonder if a key question regarding the utility of surveillance for VTE should be included. While this is not a method of prophylaxis it certainly is part of a comprehensive VTE prophylaxis program	We appreciate the reviewer's positive comments. We agree that the utility of surveillance would be an important KQ to consider in future research. This has now been included in the future research section
Public Comments - EBIR	General	We fully agree with the authors that more data are needed to answer these many questions. We also take the opportunity to reiterate that caval filters should be used sparingly and in the right patient population, but should not be avoided for those patients who truly need them. We also join the call for more research to be performed in this area.	We appreciate the comments. An updated future research section addresses many of these concerns.
Public Comments - KI	General	Mechanical Devices Cell Is there a need to differentiate or clarify TED hose from compression stockings Web site shows that TED (Thrombo-Embolic-Deterrent) anti-embolism stockings have 18mmHg compression for bedridden patients Compression stockings are optimal if ankle pressure is 30-40mmHg to prevent PTS Should ambulation be mentioned as a non-mechanical intervention, or is it unrealistic in these special populations?	We have clarified the specific interventions. Ambulation as a sole non-mechanical intervention is unrealistic in theses high risk populations. We also attempted to capture information on standard interventions but this was poorly reported in the primary studies.
Public Comments - KI	General	Editorial correction: 50% has space between 50 and % sign	This has been fixed
Public Comments - KI	General	Post-thrombotic syndrome heading: Check on accuracy of correlation of PTS (post-thrombotic syndrome) as a complication of IVC filter placement; it is usually considered a complication of DVT	We appreciate the comments and have clarified this issue
Public Comments - KI	General	Deep Vein Thrombosis and IVC Clarify IVC filters and implication that they prevent DVT; they prevent clots from entering lungs as Pes	We appreciate the comments. We agree that filters prevent PE
Public Comments - KI	General	IVC Filter heading: Clarify IVC filters and implication that they prevent DVT; they prevent clots from entering lungs as Pes	We appreciate the comments We agree that filters prevent PE.
Public Comments - KI	General	Editorial correction: Add s to increase in 2nd bullet	This has been fixed
Reviewer 1	Clarity and Usability	The results are clearly stated	Thank you
Reviewer 2	Clarity and Usability	Suggestions for improving clarity and usability above.	We have made these changes

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	Clarity and Usability	Well organized. Key points are clearly presented in the abstract and conclusions of the manuscript. Unfortunately, the strength of the data is insufficient to make any recommendations regarding the best approaches to VTE prevention in these special populations. Thus, the conclusion is perhaps self-evident ... there is a significant need for better-designed studies in these populations. In this regard the authors provide some guidance to the research community.	We agree that there is a need for better-designed studies in these populations. Our updated future research section provides guidance on the design of such studies.
Reviewer 4	Clarity and Usability	The structure is well-done and the tables are exceptional to understand the issues present in each study that makes them effective/ineffective. The amount of work is tremendous.	Thank you
Reviewer 5	Clarity and Usability	I wonder if the report is going to be useful or misinterpreted. The one sentence summary is: "We don't know anything about prophylaxis in these patients" Yet populations that are often less ill then these have demonstrated benefit in some trials, and extrapolatoins from them are hard to resist. In the face of perfect evidence, doctors and hospital improvement teams still have to decide what to do, how to structure order sets etc. This is not a criticism of the writing, just of the nature of this work. Overall very well done and thorough review.	It is difficult to summarize the contents of a complex nuanced comparative effectiveness review in a one line summary. Although the SOE is insufficient for major comparisons and outcomes, there is low SOE for several other comparisons and outcomes which may be useful for some clinicians.
Reviewer 6	Clarity and Usability	The report is well structured and clearly reported--it should inform policy makers that higher quality unbiased research is needed as is an concurrent assessment of the comparative effectiveness of prophylaxis. Clinicians, however, will be a bit disappointed that their clinical practice for prophylaxis has no substantially strong evidence to support it.	We agree that this review should inform policy makers to conduct more research given the paucity of high quality evidence for several KQs.
Reviewer 7	Clarity and Usability	Simple message = inadequate evidence for each one of the selected topics. This is the obvious reason why evidence-based clinical practice guidelines have either avoided discussion of these subtopics altogether or made low level suggestions.	We appreciate the reviewer's comments. In certain instances guidelines such as the ACCP provide recommendations on those undergoing bariatric surgery by assuming evidence from other abdominal surgeries is applicable to these special populations. In contrast we have specifically included available evidence on these specific populations and highlighted the paucity of evidence after a thorough evidence review.

Commentator & Affiliation	Section	Comment	Response
Reviewer 7	Clarity and Usability	Since the topics were chosen based on known inadequate evidence, it is not surprising that this was the conclusion of the project. The potential benefits of this review include: 1. Summarizes the current state of knowledge for each of the 8 selected subtopics in thromboprophylaxis 2. Outlines the paucity of evidence for each of these subtopics - clearly and quantitatively demonstrates what is generally already well-known 3. Useful for future researchers to be able to cite this review as support for conducting further research 4. Might be useful for guideline developers to save them some time if they choose to address the topics of these reviews	We appreciate the reviewers comments
Reviewer 7	Clarity and Usability	However, I do not see any direct usability of this review for clinical practice. On page 1, the authors state "This report should also be useful to clinicians and patients who are making decisions about the best approach to prophylaxis." Apart from non-expert clinicians becoming aware that there is little or no useful evidence for these topics, I disagree completely with this characterization of the potential benefit of these reviews.	We respect the reviewer's opinion. However we hope that this report will also be useful for clinical practice despite the limitations of the existing evidence. Clinical decisions about these populations have to be made on a daily basis. Additionally, the paucity of evidence and the need for additional research may be the most impactful outcome of this report.
Reviewer 7	Clarity and Usability	Overall, the length of this report greatly exceeds the quality of evidence found. Tables summarizing the reasons for ignoring the vast majority of poor quality studies would have saved a lot of space. The report would have been more useful if it was up to 60% shorter.	We have attempted to make the report concise by eliminating redundant text. The concise executive summary should be useful for readers
Reviewer 7	Clarity and Usability	For transparency and clarity, the Figures should also include the actual n/N data for the interventions rather than just the RR and CI and should include the p and I2 values. There remain spelling and grammar errors, incomplete references, annoying errors in linkage to tables and figures (e.g. for KQ1, all the Tables are "off" by 1 and some of the Figure references in the text are incorrect), and incorrect study years in some of the tables. Although this is not the final draft of this report, I hope the authors carefully go through the entire document to correct these errors.	We have updated the figures to include the n/N along with the relative risk and Confidence interval. We have edited the report for clarity.
Reviewer 8	Clarity and Usability	The report is well organized - for each question, it is relatively easy to find the high-level summary as well as the details on which that summary is based. Many of the conclusions will not impact clinical practice because they are based on insufficient evidence; however, we must hope that this herculean and comprehensive effort will highlight the need for resources to conduct definitive, practice-changing clinical research.	We agree that this effort should guide future research. We hope that this report will also be useful for clinical practice despite the limitations of the existing evidence.

Commentator & Affiliation	Section	Comment	Response
Reviewer 9	Clarity and Usability	In summary, authors have conducted a thorough search, identified relevant studies and drew appropriate conclusions form the limited evidence available in this area. Particularly, this report yet again highlight what has been known for years that kidney disease population are excluded from clinical trials (JAMA. 2006 Sep 20;296(11):1377-84).	We agree with the reviewers comments
Reviewer 10	Clarity and Usability	"Is the report well structured and organized?" - yes, exceedingly	Thank you
Reviewer 10	Clarity and Usability	"Are the main points clearly presented?" - yes	Thank you
Reviewer 10	Clarity and Usability	"Can the conclusions be used to inform policy and/or practice decisions?" - not really. The conclusions all state that the evidence is low or insufficient and the authors cannot make any recommendations to help guide clinicians	Our CER is not intended to make recommendations. The evidence will be useful to inform clinicians and policy makers. Given the low or insufficient SOE for several outcomes future research is a high priority
Reviewer 11	Clarity and Usability	The report is well structured.	Thank you
Reviewer 12	Clarity and Usability	Yes to all questions. The report is well structured and organized. Impressive review	Thank you
Reviewer 14	Clarity and Usability	The report is extremely detailed and logically organized. I think the primary conclusions are clearly stated and the authors clearly identify what research questions warrant additional investigation.	Thank you
Reviewer 15	Clarity and Usability	Completely unusable and unclear as currently written. Clinicians would not know how to read, where to look and what to take home. The need to be simplified and cleaned up a lot. The tremendous redundancy needs to be removed. Perhaps dividing up into a series of paper would increase clarity.	We have edited the report for clarity and divided it into several sections by KQs. The report will be translated into easily readable summaries for clinicians by KQs. We will also be publishing separate manuscripts by KQs
Reviewer 16	Clarity and Usability	This report is one of the best reviews of this special population that I have read. This data will allow an opportunity to develop quality and safety projects as well as clinical research.	Thank you
Reviewer 17	Clarity and Usability	Definitely well structured. points are clearly presented	Thank you